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(54) Title: INCLUSION COMPLEX CONTAINING INDOLE SELECTIVE SEROTONIN AGONIST

(57) Abstract

An inclusion complex comprises (a) an indole selective serotonin (5-HT_{1D}) agonist or a pharmaceutically acceptable salt thereof, such as for example sumatriptan, and (b) unsubstituted or substituted beta- or gamma-cyclodextrin, such as for example methyl-beta-cyclodextrin. Pharmaceutical compositions containing the inclusion complex and the use of the inclusion complex in the treatment of migraine and cluster headaches are also disclosed.

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INCLUSION COMPLEX CONTAINING INDOLE SELECTIVE SEROTONIN AGONIST

BACKGROUND OF THE INVENTION

THIS invention relates to an inclusion complex of an indole selective serotonin ($5\text{-}HT_{1D}$) agonist and an unsubstituted or substituted beta- or gamma-cyclodextrin, and to pharmaceutical compositions containing such a complex, particularly for oral or nasal mucosal delivery, for the treatment of migraine or cluster headaches.

Sumatriptan (3-(2-dimethylaminoethyl)indol-5-yl-N-methylmethanesulphonamide) and other structurally related indole derivatives such as naratriptan, rizatriptan, zolmitriptan, eletriptan and almotriptan are selective serotonin ($5\text{-}HT_{1D}$) agonists useful for the treatment of migraine. Sumatriptan is given orally or subcutaneously as the succinate salt for the treatment of migraine. Sumatriptan is rapidly absorbed following oral administration and undergoes extensive pre-systemic metabolism,

resulting in a low bioavailability of about 14%. The bioavailability following subcutaneous administration is 96%. For the acute treatment of migraine, sumatriptan may be given in an initial dose of 100mg by mouth and a clinical response can be expected between 0,5 to 2 hours. Alternatively, sumatriptan may be given by subcutaneous injection in a single dose of 6 mg with a clinical response in 10 - 15 minutes.

Apart from the low bioavailability following oral administration of anti-migraine compounds such as sumatriptan, the classical oral route of administration has limitations in the treatment of migraine due to nausea and vomiting associated with migraine attacks. Many patients are averse to self administration by subcutaneous injection, limiting this route of administration.

The oral and nasal cavities have several advantages as sites for systemic drug delivery, particularly avoidance of presystemic metabolism. However, the low permeability of the membranes that line the oral and nasal cavities result in a low flux of drug. There is therefore a need to enhance drug penetration to improve bioavailability following oral or nasal mucosal drug delivery.

There are several methods known in the art to deliver drugs to the oral and nasal mucosae. These include buccal and sublingual tablets or lozenges, adhesive patches, gels, solutions or sprays (powder, liquid or aerosol) for the oral cavity and solutions or sprays (powder, liquid or aerosol) for the nasal cavity.

The absorption of drugs from mucosal membranes may be enhanced by (i) increasing drug solubility, (ii) pH modification to favour the unionized form of the drug, (iii) addition of mucoadhesive agents to improve contact between the delivery system and the membrane and (iv) incorporation of so-called penetration enhancers.

There are a number of penetration enhancers known to influence the permeability of drugs across epithelial membranes [for a recent review see Walker, R.B and Smith, E.W. Advanced Drug Delivery Reviews 1996, 18, 295-301].

Cyclodextrins and their derivatives have found extensive application as solubilizers and stabilizers due to their ability to form inclusion complexes with a wide variety of compounds [see (J. Szejtli, *Cyclodextrin Technology*, Kluwer Academic Press) and (J. Szejtli & K-H Fromming, *Cyclodextrins in Pharmacy*, Kluwer Academic Press)]. Cyclodextrins have been used to enhance intestinal absorption of drugs primarily through increasing solubility. Recently, cyclodextrins have been shown to have positive and negative effects on transdermal penetration of drugs [see (Loftsson, T. et al International Journal of Pharmaceutics 1995, 115, 255-258), (Vollmer, U. et al. International Journal of Pharmaceutics 1993, 99, 51-58), (Legendre, J.Y. et al. European Journal of Pharmaceutical Sciences 1995, 3, 311-322) and (Vollmer, U. et al Journal of Pharmacy and Pharmacology 1994, 46, 19-22)]. Cyclodextrins may improve nasal absorption of drugs [see (Merkus, F.W. et al. Pharmaceutical Research 1991, 8, 588-592) and (Shao, Z. et al Pharmaceutical Research 1992, 9, 1157-1163)] and enhance absorption from sublingual administration of drug/cyclodextrin complexes. Cyclodextrins also protect nasal mucosal damage by penetration enhancers [see Jabbal-Gill, I. et al. European Journal of Pharmaceutical Sciences 1994, 1(5), 229-236]

Cyclodextrins are water soluble cone-shaped cyclic oligosaccharides containing 6, 7 or 8 glucopyranose units. The interior or "cavity" of the cone is hydrophobic whilst the exterior is hydrophilic. The size of the cavity increases with increasing number of glucose units. Several cyclodextrin derivatives such as alkyl, hydroxyalkyl and sulfoalkyl ethers have been prepared with improved solubility [see (J. Szejtli & K-H Fromming, *Cyclodextrins in Pharmacy*, Kluwer Academic Press) and (Stella, V.J. et al

Pharmaceutical Research 1995, 12 (9) S205)]. Suitably sized hydrophobic "guest" molecules may enter the "host" cavity to form a classical host-guest "inclusion compound" or "inclusion complex" with either the entire guest molecule included or only a portion thereof. The driving mechanism for cyclodextrin inclusion complexation is the affinity of the hydrophobic guest molecule for the cavity of the cyclodextrin host molecule with displacement of cavity water molecules to a thermodynamically more stable state. The term "complex stability" or stability of a given inclusion complex refers to the association/dissociation equilibrium of host and guest in solution. Complex stability depends on the number of intermolecular bonding interactions between the host and guest. Van der waals forces and hydrophobic interactions are the main interactions stabilizing inclusion complexes (Bergeron, R.J. et al. *Journal of the American Chemical Society* 1977, 99, 5146). Depending on the nature and position of hydrogen bonding functionalities on a given guest, there may be hydrogen bonding between the guest and hydroxyl groups of the cyclodextrin or other hydrogen bonding groups in the case of cyclodextrin derivatives. Ionic interactions between the host and guest are also possible in the case of ionic cyclodextrins such as sulphobutyl ethers (Stella, V.J. et al Pharmaceutical Research 1995, 12 (9) S205).

Cyclodextrin inclusion complexes may be prepared on the basis of liquid state, solid state or semi-solid state reaction between the components (J. Szejtli, *Cyclodextrin Technology*, Kluwer Academic Press). The first is accomplished by dissolving the cyclodextrin and guest in a suitable solvent or mixture of solvents and subsequently isolating the solid state complex by crystallization, evaporation, spray drying or freeze drying. In the solid state method, the two components may be screened to uniform particle size and thoroughly mixed whereafter they are ground in a high energy mill with optional heating, screened and homogenized. In the semi-solid state, the two components are kneaded in the presence of small amounts of a suitable solvent, and the complex so-formed, is dried, screened and homogenized.

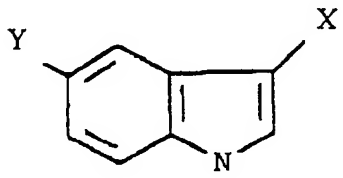
The liquid state reaction generally provides optimum conditions for completeness of reaction. Depending on solvent conditions, the dissolved inclusion complex exists in equilibrium between uncomplexed host and guest and complexed host/guest.

SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided an inclusion complex of (a) an indole selective serotonin (5-HT_{1D}) agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta- or gamma- cyclodextrin.

By an indole selective serotonin (5-HT_{1D}) agonist there is meant a compound which includes the indole structure, which structure will generally be substituted, and which has selective serotonin (5-HT_{1D}) agonist activity.

The indole selective serotonin (5-HT_{1D}) agonist is preferably selected from compounds having the formula:



wherein X and Y represent suitable substitutions, more preferably from the group consisting of sumatriptan, naratriptan, rizatriptan, zolmitriptan, eletriptan and almotriptan or a pharmaceutically acceptable salt thereof. Thus, compound (a) may be used in the form of the free base or in the form of a pharmaceutically acceptable salt such as a hydrochloride, succinate, citrate, fumarate, sulphate, benzoate, or maleate salt.

The inclusion complex preferably has a stoichiometry of (a) to (b) of 1:1

mol/mol.

The inclusion complex is preferably an inclusion complex of sumatriptan free base and methyl-beta-cyclodextrin or of sumatriptan succinate and methyl-beta-cyclodextrin which has substantially the X-ray powder diffraction pattern of Figure 4 or Figure 5.

According to a second aspect of the invention there is provided a pharmaceutical composition which comprises as an active ingredient an inclusion complex of (a) an indole selective serotonin (5-HT_{1D}) agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta- or gamma-cyclodextrin.

The pharmaceutical composition is preferably for use in the treatment of migraine and cluster headaches.

The pharmaceutical composition is preferably adapted for oral or nasal mucosal delivery.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described in more detail, by way of example only, with reference to the accompanying drawings in which:

Figure 1 shows a differential scanning calorimetry thermogram of sumatriptan succinate with the onset melting temperature of 166°C and sharp endothermic melting peak at 167,9°C;

Figure 2 shows a differential scanning calorimetry thermogram of a 1:1 kneaded complex of sumatriptan succinate and methyl-beta-cyclodextrin obtained from Example 1;

Figure 3 shows a differential scanning calorimetry thermogram of a 1:1 kneaded complex of sumatriptan succinate and methyl-beta-cyclodextrin containing 1 molar equivalent of tromethamine obtained from Example 2;

Figure 4 shows an X-ray powder diffraction pattern of the 1:1 kneaded complex of sumatriptan succinate and methyl-beta-cyclodextrin obtained from Example 1;

Figure 5 shows an X-ray powder diffraction pattern of the 1:1 kneaded complex of sumatriptan succinate and methyl-beta-cyclodextrin containing one molar equivalent of tromethamine obtained from Example 2; and

Figure 6 shows a cut-away perspective of the geometry optimized molecular mechanical model of an inclusion complex of sumatriptan (pale grey) in beta-cyclodextrin (dark grey).

DESCRIPTION OF EMBODIMENTS

The crux of the invention is an inclusion complex of (a) an indole selective serotonin (5-HT_{1D}) agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta- or gamma-cyclodextrin.

Examples of suitable compounds (a) are sumatriptan, naratriptan, rizatriptan, zolmitriptan, eletriptan and almotriptan. The compound may be used in the form of the free base or in the form of a pharmaceutically acceptable salt such as a hydrochloride, succinate, citrate, fumarate, sulphate, benzoate, or maleate salt or the like.

The second component of the inclusion complex is an unsubstituted or

substituted beta- or gamma-cyclodextrin.

Highly water soluble cyclodextrins such as 2-hydroxypropylated or methylated or sulphoalkylated derivatives of beta-cyclodextrin are the preferred cyclodextrins of the invention. Gamma-cyclodextrin or 2-hydroxypropylated or methylated or sulphoalkylated derivatives of gamma-cyclodextrin may also be used in the same manner as the corresponding preferred beta-cyclodextrin derivatives. The degree of substitution of the cyclodextrin derivatives may vary between 1 to 20 substituents per cyclodextrin molecule but more preferably between 3 to 15 substituents per cyclodextrin molecule. When the cyclodextrin is 2-hydroxypropyl-beta-cyclodextrin, the preferred degree of substitution is between 3.9 and 5.1 hydroxypropyl groups per cyclodextrin molecule. When the cyclodextrin is methyl-beta-cyclodextrin, the preferred degree of substitution is between 1.8 and 2 methyl groups per glucose unit.

The inclusion complex of the invention may be prepared from aqueous solutions, slurries or pastes of the indole derivative and cyclodextrin according to conventional methods. The molar ratio of indole derivative to cyclodextrin may vary between 1:1 to 1:10 but more preferably between 1:1 to 1:5. Solutions are prepared by dissolving the cyclodextrin in a sufficient quantity of purified deionised water which may be optionally buffered between pH 7,4 to 8,5. The indole derivative is added to the solution with stirring until dissolved. The solution may be used in the preparation of liquid delivery systems such as drops, sprays or aerosols. Where a solid inclusion complex is desired, the solution or slurry may be dried by spray drying or freeze drying.

Alternatively, the indole derivative and cyclodextrin are mixed. The powder mixture is wetted with water, optionally containing a buffer pH 7,4 - 8,5, while mixing vigorously until a paste is formed. The paste is mixed for 0,25 to 2 hours and dried in an oven or in vacuo at elevated temperature. The

dried complex is crushed and sieved to the desired particle size.

A pharmaceutically acceptable buffer, capable of buffering in the pH range 7.4 - 8,5 may be used in the formation of the inclusion complex, particularly when the indole derivative is present as a salt. Preferred buffers include tromethamine, triethanolamine, diethanolamine. phosphate buffer, sodium bicarbonate, and sodium carbonate. The concentration of the buffer may vary from 0,5 to 5 molar equivalents relative to the indole.

The second aspect of the invention is a pharmaceutical composition which comprises as an active ingredient an inclusion complex as described above.

The pharmaceutical composition of the invention is of particular application in the treatment of migraine and cluster headaches.

Further, the pharmaceutical composition of the invention is preferably adapted for oral or nasal mucosal delivery.

The administration of an anti-migraine drug through the mucosal tissue of the nose or mouth avoids the problems associated with administration of indole serotonin agonists by injection (i.e. patient aversion and painful administration) and oral administration (i.e. slow onset of action, low bio-availability and poor compliance due to nausea and vomiting associated with migraines).

Absorption of the drug from the pharmaceutical composition of the invention is rapid such that the drug reaches the systemic circulation almost as fast as through injection and appreciably faster than oral administration, which is highly advantageous for the rapid relief of migraine attack or cluster headache.

Further, the unpleasant taste and irritant properties of the active principle are

reduced by presenting the drug to the nasal or oral mucosal membranes in the form of a cyclodextrin inclusion complex.

The present invention achieves these advantages by molecular encapsulation of the anti-migraine indole drug in a cyclodextrin, so forming a molecular inclusion complex which may be used in the solid form for the preparation of sublingual or buccal tablets, buccal patches or nasal inhalation powders (insufflations). The inclusion complex may be used in the liquid state for the preparation of metered dose sprays, drops or pressurized aerosols for nasal or oral administration. The complex according to the invention may be incorporated into a shearform matrix designed for immediate release as described in Fuisz Technologies Ltd patents (Eur. Pat. Appl. EP 95-650038 and PCT Int. Appl. WO 95/34293).

According to the invention, the indole nucleus of selective serotonin ($5\text{-}HT_{1D}$) agonists has been found to be readily included in the cavity of beta-cyclodextrins such as hydroxypropyl-beta-cyclodextrin and methyl-beta-cyclodextrin to form molecular inclusion complexes with a 1:1 mol/mol stoichiometry. Inclusion complexes of a variety of indole-based serotonin agonists may therefore be prepared according to methods known in the art such as spray drying, freeze drying and kneading, as described above. The complexes according to the invention may also be incorporated into microspheres by methods appreciated in the art. The complexes according to the invention are stable, amorphous and highly water soluble.

Penetration enhancers may be used to promote the passage of the indole derivative across the mucosal membranes. Typical permeation enhancers include fatty acids and their salts such as sodium caprate, sodium caprylate and sodium oleate, sodium laurate, and bile salts such as sodium glycodeoxycholate, sodium glycocholate, sodium cholate and sodium taurodeoxycholate. Other penetration enhancers may include tensides, ionic surfactants such as sodium lauryl sulphate, or non-ionic surfactants such as

polyethylene glycol 660 hydroxystearate or polyoxyethylene lauryl ethers, fusidates such as sodium taurodihydrofusidate. Other specific enhancers include azone and chitosan. Combinations of permeation enhancers such as polyoxyethylene 8 lauryl ether and sodium glycocholate or mixed micelles such as sodium caprate and sodium glycocholate may also be used. The penetration enhancers may also be used in combination with beta or gamma-cyclodextrins or their methyl, hydroxypropyl or sulphoalkyl derivatives. Typical concentrations of permeation enhancers are between 0,1 % to 5%, more preferably between 0,25% to 3% by weight of the composition.

As stated above, the serotonin (5-HT_{1D}) agonist may be used in the form of the free base or a pharmaceutically acceptable salt. When acidic penetration enhancing excipients are used such as bile acids or fatty acids or pharmaceutically acceptable salts of bile acids or fatty acids, salt formation between the basic component of the serotonin (5-HT_{1D}) agonists and the acidic component of the bile or fatty acid may occur.

Buffering agents may be incorporated into the pharmaceutical composition of the invention to control the microenvironmental pH surrounding the drug delivery system in the alkaline range, so as to maximize the percentage of the unionized form of the drug. Drugs in the unionized form cross mucosal membranes more readily than the corresponding unionized form.

Liquid compositions suitable for nasal or oral administration may contain a suitable quantity of viscosity modifying agents such as hypromellose or carbopol 934P and preservative agents such as chlorhexidine gluconate or thiomersal.

Oral compositions may contain suitable flavouring and sweetening agents such as cherry, mint, spearmint, vanilla, aspartame, sucrose, xylitol, saccharin and the like.

Typical sublingual or buccal tablets may include lubricants such as magnesium stearate, calcium stearate and sodium stearyl fumarate to facilitate tablet compression, diluents such as lactose, microcrystalline cellulose, maize starch and the like and mucoadhesive agents such as chitosan, carbopol 934P, and hydroxypropylcellulose and the like.

Typical disintegrants to enhance sublingual tablet disintegration may include sodium carboxymethylcellulose, sodium starch glycolate, polyplasdone XL, and dried starch.

The following examples illustrate the present invention.

EXAMPLE 1

Sumatriptan succinate (1g) and methyl-beta-cyclodextrin (3,18) are mixed in a mortar. Purified deionised water (2ml) is added in aliquots with mixing to form a uniform paste. Mixing is continued for 0.5 hours and the paste is transferred to a vacuum oven and dried at 40°C and 5 millibar. The dried complex is crushed with a pestle and passed through a 60 mesh (250 micron) sieve. The complex contains 23,0 % m/m (mass/mass) sumatriptan succinate as determined by HPLC.

EXAMPLE 2

Tromethamine (0,293g) was dissolved in 5 ml purified deionised water. Sumatriptan succinate (1g) and methyl-beta-cyclodextrin (3,18g) are mixed in a mortar. The tromethamine solution is added in aliquots with mixing to form a uniform paste. Mixing is continued for 0,5 hours and the paste is transferred to a vacuum oven and dried at 40°C and 5 millibar. The dried complex is crushed with a pestle and passed through a 60 mesh (250 micron) sieve. The complex contains 21,7 % m/m sumatriptan succinate as determined by HPLC.

EXAMPLE 3

The unit composition of a sublingual tablet containing the equivalent of 20 mg sumatriptan base is as follows:

Sumatriptan/methyl-beta-cyclodextrin complex (from Example 2)	130mg
Lactose NF	20mg
Magnesium stearate	1mg

The complex is blended with the lactose. The lubricant is screened in and the mixture is blended and formed into sublingual tablets by compression at 10 - 30N.

EXAMPLE 4

The unit composition of a sublingual tablet containing the equivalent of 20 mg sumatriptan base is as follows:

Sumatriptan/methyl-beta-cyclodextrin complex (from Example 1)	122mg
Xylitol	28mg
Sodium caprate	3.75mg
Magnesium stearate	1mg

The complex is blended with the xylitol and sodium caprate. The lubricant is screened in and the mixture is blended and formed into sublingual tablets by compression at 10 - 30N.

EXAMPLE 5

Hydroxypropyl-beta-cyclodextrin (3,39g) is dissolved in purified deionised water (8ml) buffered to pH 7,4 with phosphate buffer. Sumatriptan succinate (1g) is added to the solution with stirring. The solution is stirred for 20

minutes and then sodium caprate (25mg) and chlorhexidine gluconate (0,01%) is added. The volume is adjusted to 10 ml by addition of phosphate buffer pH 7,4 and the tonicity of the final solution is adjusted with sodium chloride to 300 mOsm/kg. The solution is filtered and filled into a metered dose nasal spray bottle. Each 0,1 ml metered dose contains 10 mg sumatriptan succinate suitable for nasal administration.

Referring now to the drawings, Figure 1 shows a differential scanning calorimetry thermogram of sumatriptan succinate with the onset melting temperature of 166°C and sharp endothermic melting peak at 167,9°C. The thermogram was recorded on a Perkin-Elmer DSC7 calorimeter with a heating rate of 5°C per minute. A sample mass of 1,36 mg was used.

Figure 2 shows a differential scanning calorimetry thermogram of a 1:1 kneaded complex of sumatriptan succinate and methyl-beta-cyclodextrin obtained from Example 1. The characteristic melting endotherm of sumatriptan succinate shown in Figure 1 is absent, providing evidence of inclusion complexation between sumatriptan and methyl-beta-cyclodextrin. Characteristic decomposition of methyl-beta-cyclodextrin is seen from 175°C. Experimental conditions where as described in Example 1, except that a sample mass of 11,1 mg was used to provide a sumatriptan succinate response equivalent to Example 1.

Figure 3 shows a differential scanning calorimetry thermogram of a 1:1 kneaded complex of sumatriptan succinate and methyl-beta-cyclodextrin containing 1 molar equivalent of tromethamine obtained from Example 2. The characteristic melting endothermy of sumatriptan succinate shown in Figure 1 is absent. An endotherm corresponding to the free base at 89°C is also absent providing evidence of inclusion complexation between sumatriptan and methyl-beta-cyclodextrin. Characteristic decomposition of methyl-beta-cyclodextrin is seen from 175°C. Experimental conditions were as described in Example 1 except that a sample mass of 12,42 mg was used

to provide a sumatriptan succinate response equivalent to Example 1.

Figure 4 shows an X-ray powder diffraction pattern of the 1:1 kneaded complex of sumatriptan succinate and methyl-beta-cyclodextrin obtained from Example 1. The absence of resolved sharp peaks characteristic of crystalline sumatriptan succinate indicates inclusion complexation with resultant loss of crystallinity. The resulting diffraction pattern is characteristic of an amorphous solid.

Figure 5 shows an X-ray powder diffraction pattern of the 1:1 kneaded complex of sumatriptan succinate and methyl-beta-cyclodextrin containing 1 molar equivalent of tromethamine obtained from Example 2. The absence of resolved sharp peaks characteristic of crystalline sumatriptan succinate and tromethamine indicates inclusion complexation with resultant loss of crystallinity. The resulting diffraction pattern is characteristic of an amorphous solid.

Figure 6 shows a cut-away perspective of the geometry optimised molecular mechanical model of an inclusion complex of sumatriptan (pale grey) in beta-cyclodextrin (dark grey). The indole nucleus fills the cavity with the pendant dimethylaminoethyl (bottom) and methanesulphonamide (top) side chains extending out of the cavity.

CLAIMS

1 An inclusion complex of (a) an indole selective serotonin (5-HT_{1D}) agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta-or gamma-cyclodextrin.

2 An inclusion complex according to claim 1 wherein (a) is sumatriptan or a pharmaceutically acceptable salt thereof.

3 An inclusion complex according to claim 1 wherein (a) is selected from the group consisting of naratriptan, rizatriptan, zolmitriptan, eletriptan and almotriptan and the pharmaceutically acceptable salts thereof.

4 An inclusion complex according to any one of claims 1 to 3 wherein (b) is selected from the group consisting of 2-hydroxypropyl-beta-cyclodextrin, a methylated-beta-cyclodextrin, and a sulphoalkylated beta-cyclodextrin.

5 An inclusion complex according to any one of claims 1 to 4 wherein (b) has a degree of substitution between 1 to 20 substituents per cyclodextrin molecule.

6 An inclusion complex according to claim 5 wherein (b) has a degree of substitution between 3 to 15 substituents per cyclodextrin molecule.

7 An inclusion complex according to any one of claims 1 to 3 wherein (b) is 2-hydroxypropyl beta-cyclodextrin with a degree of substitution between 3,9 and 5,1 hydroxypropyl groups per cyclodextrin molecule.

8 An inclusion complex according to any one of claims 1 to 3 where (b) is methyl-beta-cyclodextrin with a degree of substitution between 1.8 and 2 methyl groups per glucose unit.

9 An inclusion complex of sumatriptan free base and methyl-beta-cyclodextrin.

10 An inclusion complex of sumatriptan succinate and methyl-beta-cyclodextrin.

11 An inclusion complex of sumatriptan succinate and methyl-beta-cyclodextrin having substantially the X-ray powder diffraction pattern of Figure 4 or Figure 5.

12 An inclusion complex according to any one of claims 1 to 11 wherein the inclusion complex has a stoichiometry of (a) to (b) of 1:1 mol/mol.

13 A pharmaceutical composition comprises as an active ingredient an inclusion complex of (a) an indole selective serotonin ($5\text{-}HT_{1D}$) agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta- or gamma-cyclodextrin.

14 A pharmaceutical composition according to claim 13 wherein the inclusion complex is as defined in any one of claims 2 to 12.

15 A pharmaceutical composition according to claim 13 or claim 14 for use in the treatment of migraine or cluster headaches.

16 A pharmaceutical composition according to any one of claims 13 to 15 formulated for oral or nasal mucosal delivery.

17 The use of an inclusion complex of (a) an indole selective serotonin ($5\text{-}HT_{1D}$) agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta- or gamma-cyclodextrin in the manufacture of a medicament for use in the treatment of migraine or cluster headaches.

18 The use according to claim 17 wherein the inclusion complex is as defined in any one of claims 2 to 12.

FIGURE 1

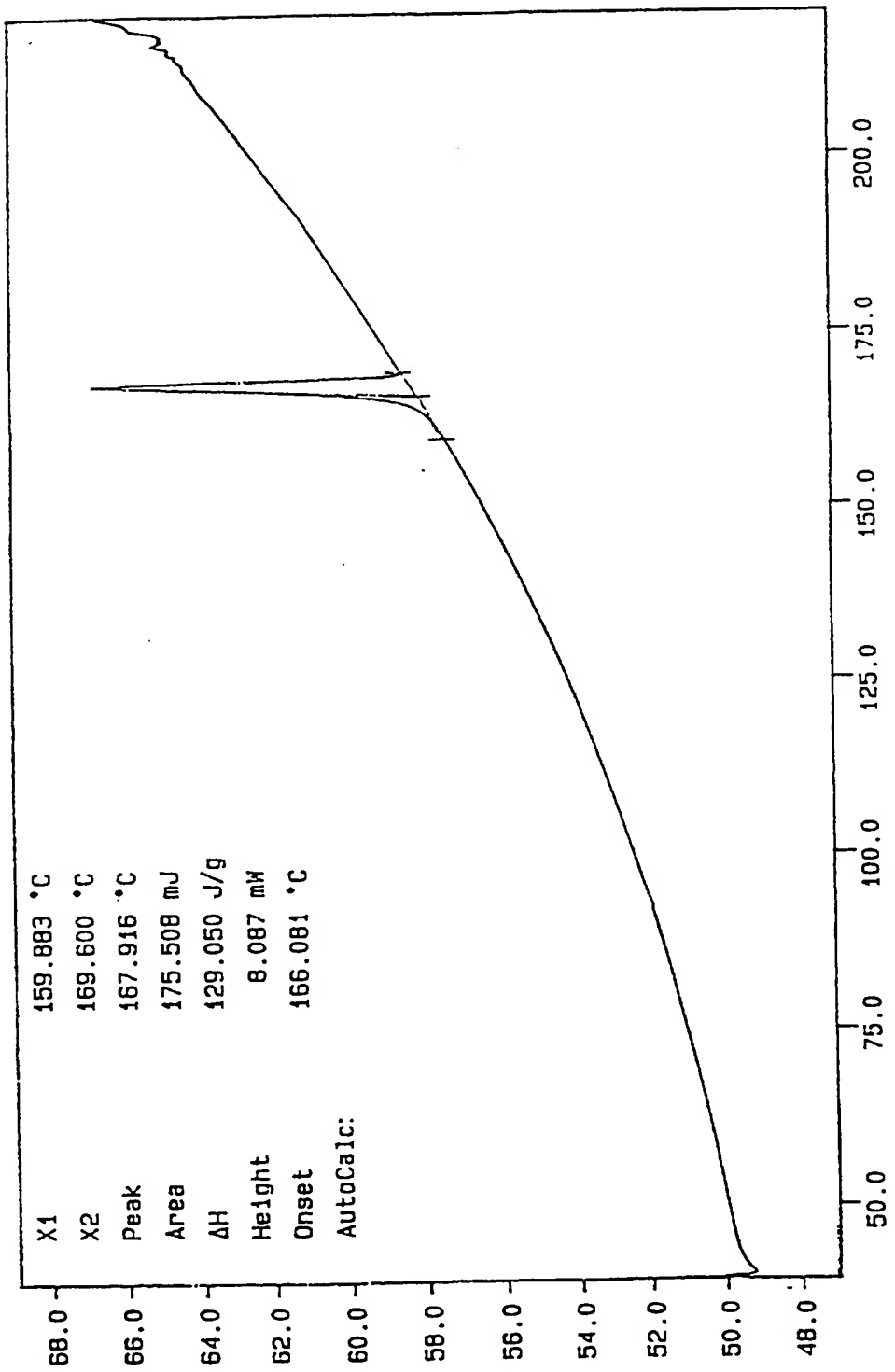

Heat flow (mW)
X1 159.883 °C
X2 169.600 °C
Peak 167.916 °C
Area 175.508 mJ
ΔH 129.050 J/g
Height 8.087 mW
Onset 166.081 °C
AutoCalc:
68.0
66.0
64.0
62.0
60.0
58.0
56.0
54.0
52.0
50.0
48.0
50.0
75.0
100.0
125.0
150.0
175.0
200.0

FIGURE 2

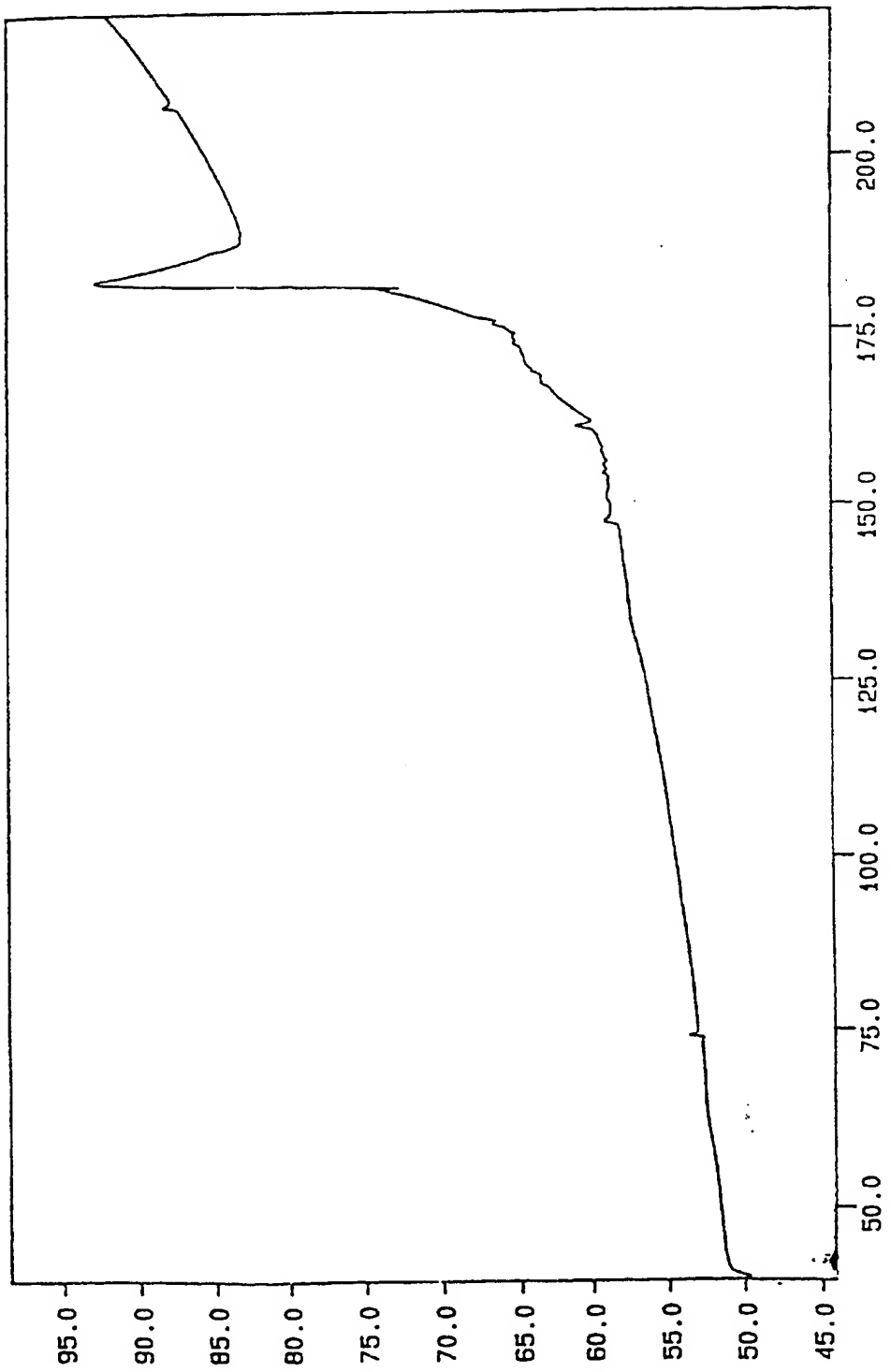

Heat Flow (mW)
95.0
90.0
85.0
80.0
75.0
70.0
65.0
60.0
55.0
50.0
45.0
50.0
75.0
100.0
125.0
150.0
175.0
200.0

FIGURE 3

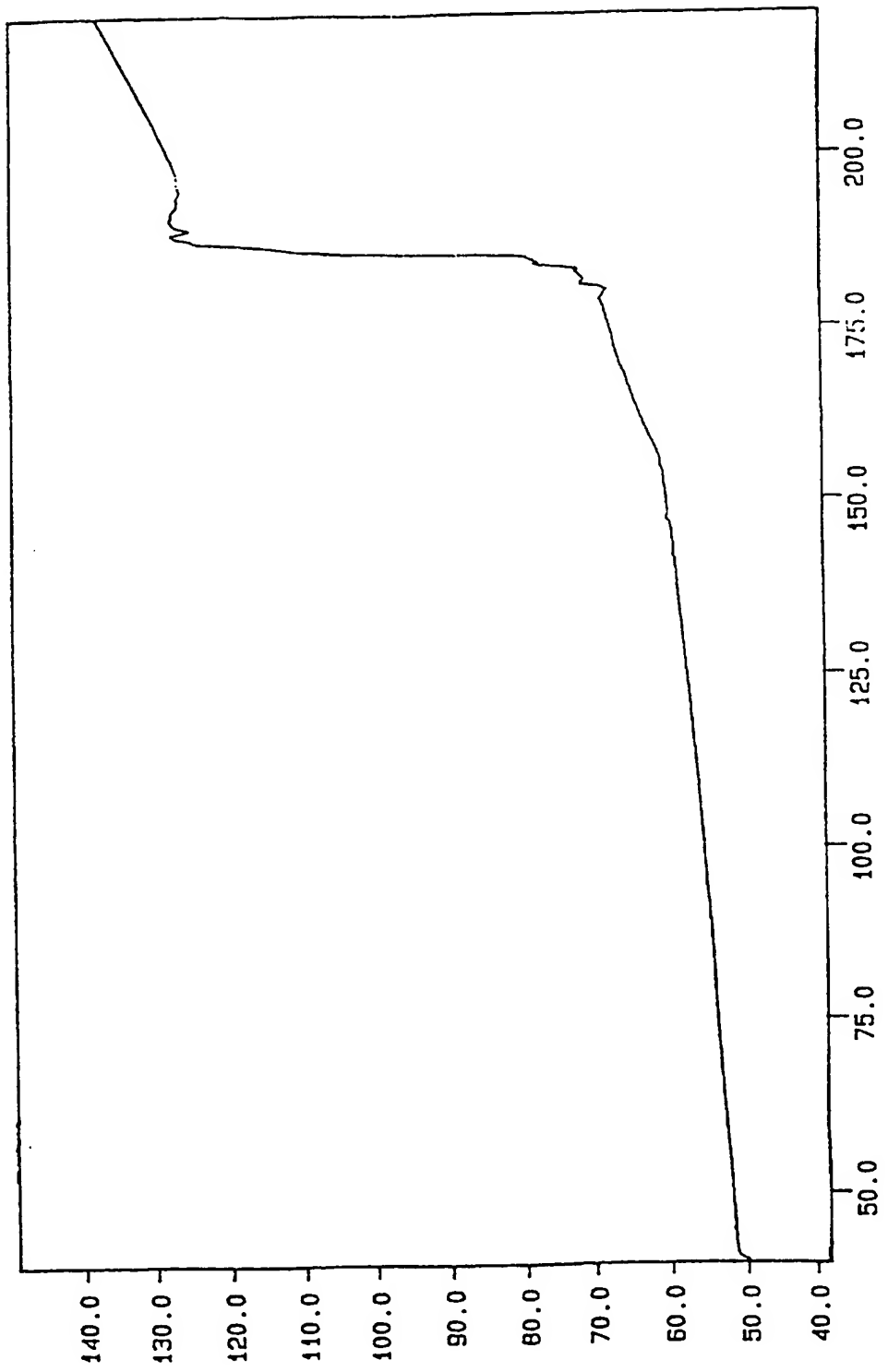

Heat Flow (mW)
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
50.0
75.0
100.0
125.0
150.0
175.0
200.0

FIGURE 4

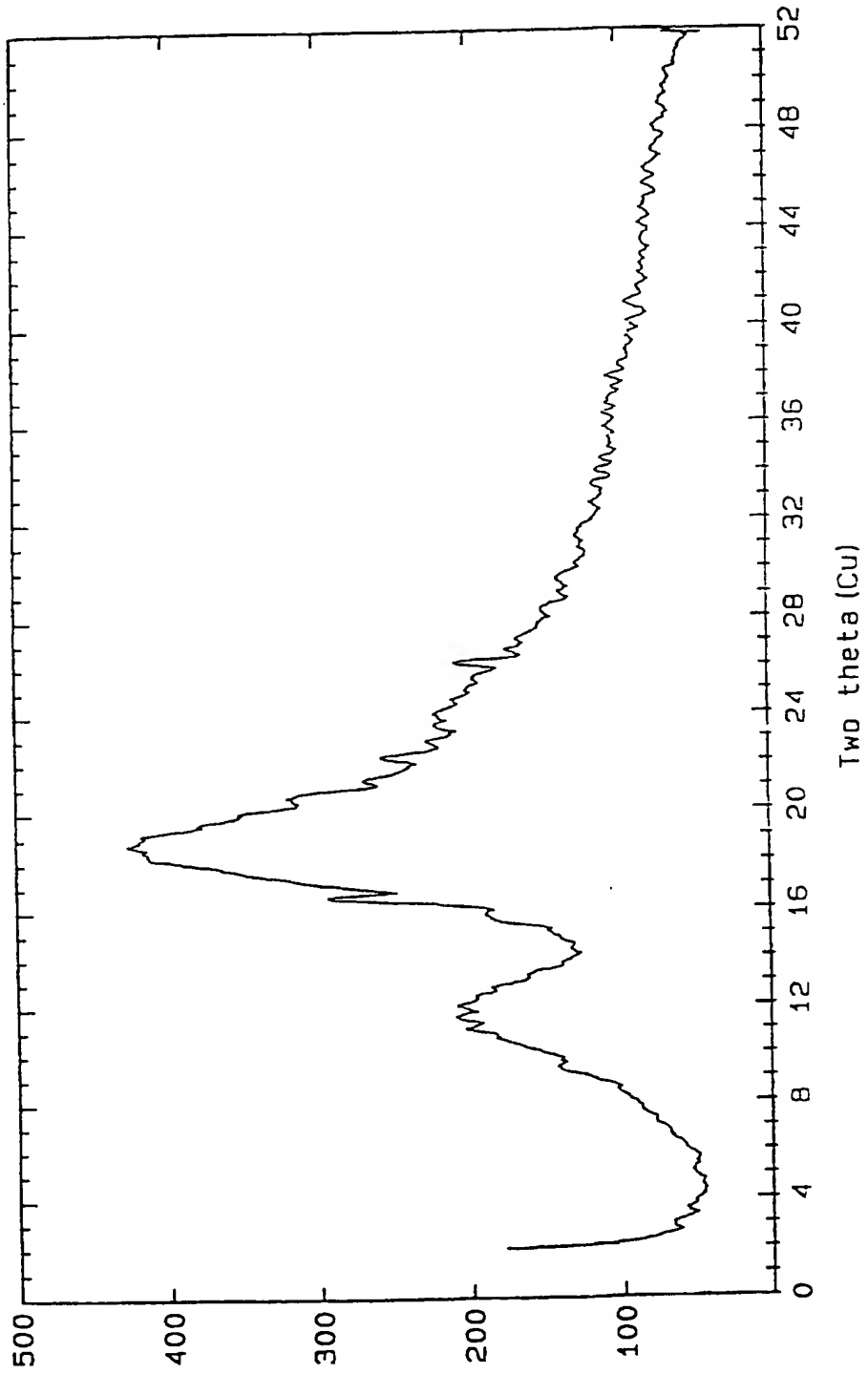
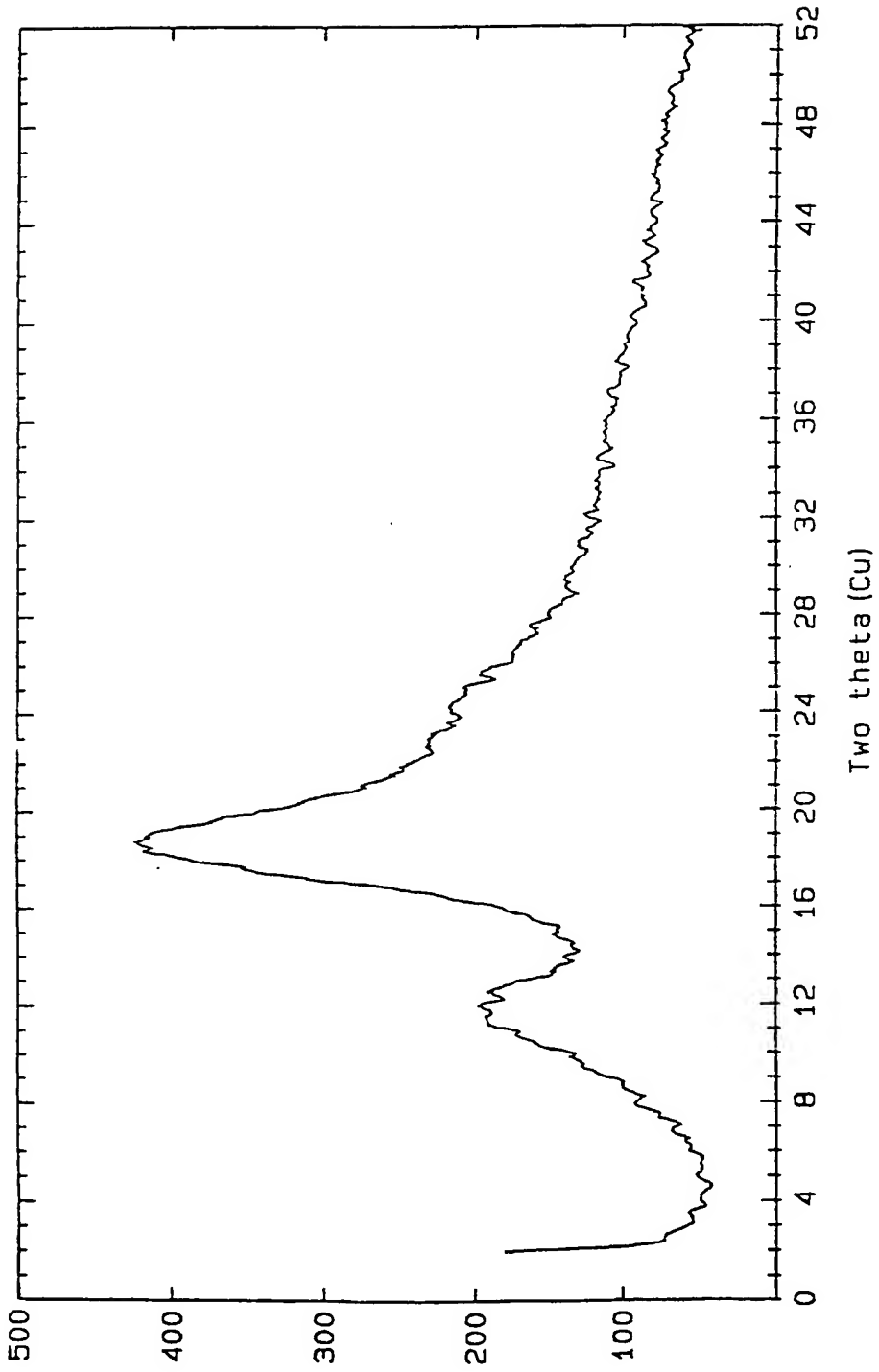

Intensity (cps)
500
400
300
200
100
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Two theta (Cu)

FIGURE 5


Intensity (cps)
500
400
300
200
100
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Two theta (Cu)

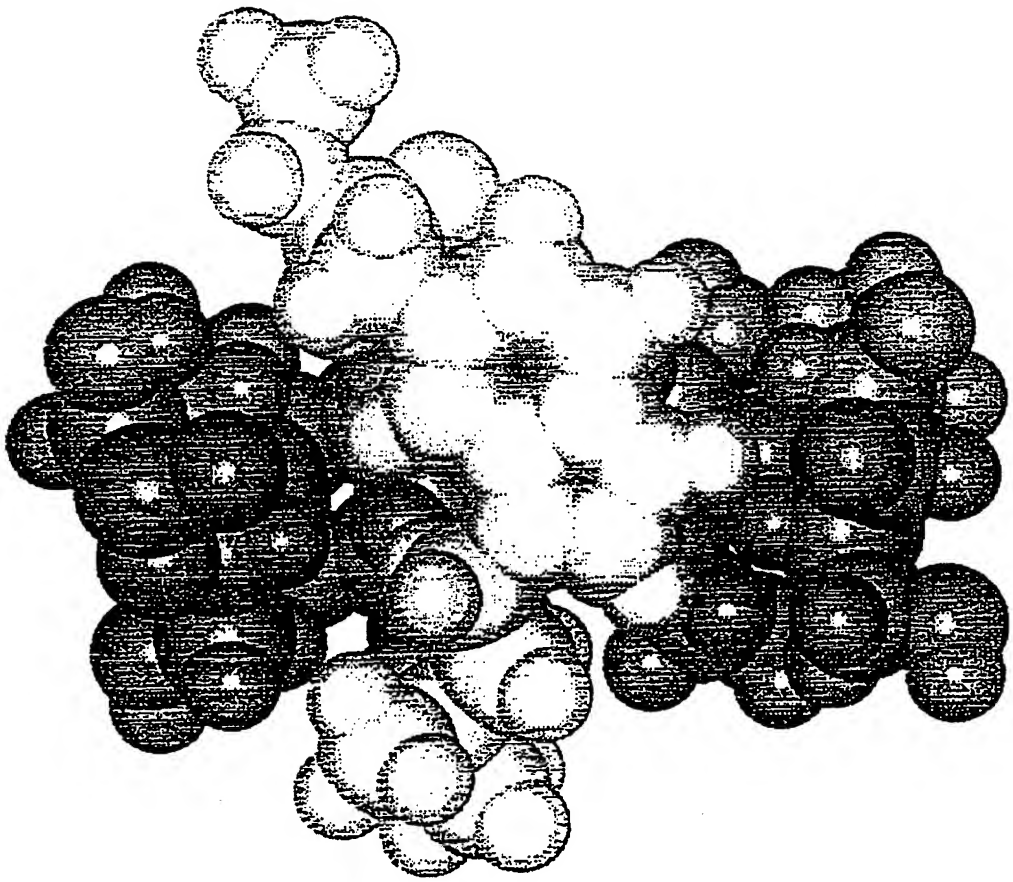


FIGURE 6

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/01872

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EVANS, ROGER G. ET AL: "Effects of 5-HT-receptor and.alpha.2-adrenoceptor ligands on the hemodynamic response to acute central hypovolemia in conscious rabbits" BR. J. PHARMACOL. (1993), 109(1), 37-47 CODEN: BJPCBM;ISSN: 0007-1188, 1993, XP002047442 see page 38, column 1, paragraph 3 ---	1-18
A	US 5 288 498 A (STANLEY THEODORE H ET AL) 22 February 1994 see claims 1,154,191 ---	1-18
A	US 5 288 497 A (STANLEY THEODORE H ET AL) 22 February 1994 see claims 1,167,203 -----	1-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 November 1997	11/12/1997

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Berte, M

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PCT/GB 97/01872

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 97/01872

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 0404205 A	27-12-90
		US 4863737 A	05-09-89
		US 4885173 A	05-12-89
		WO 9103099 A	07-03-91
		WO 9103234 A	21-03-91
		US 5484602 A	16-01-96
		US 5132114 A	21-07-92
		US 5122127 A	16-06-92
		US 5288498 A	22-02-94